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Thomas Jovin

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EXAMINER

STRZELECKA, TERESA E

ART UNIT

PAPER NUMBER

1637

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/568,038	Applicant(s) JOVIN ET AL.	
	Examiner TERESA E. STRZELECKA	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 January 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This office action is in response to an amendment filed January 6, 2009. Claims 1-13 were previously pending. Applicants amended claim 1. Claims 1-13 are pending and will be examined.
2. Applicants' arguments overcame the rejection of claim 1-13 under 35 U.S.C. 112, second paragraph. All other the previously presented rejections are maintained for reasons given in the "Response to Arguments" below.

Response to Arguments

3. Applicant's arguments filed January 6, 2009 have been fully considered but they are not persuasive.

A) Regarding the rejection of claims 1-13 under 35 U.S.C. 112, first paragraph, enablement, Applicants argue the following:

i) FRET imaging has been extensively studied and developed, as evidenced by a list of references and patents.

ii) The methods of determining relaxation kinetics are known.

iii) The instant invention "...is based on an *inversion of the principles of application of conventional measurements of relaxation kinetics*. As explained, in conventional methods the position of equilibrium of a reaction is changed by a variation of an intensive thermodynamic quantity and the relaxation of concentrations into the new equilibrium state is observed. However, with the present invention the relative concentrations of the species involved are suddenly changed (by switching the photochromic FRET acceptor from its first photochromic state into its second photochromic state) and their return into the (thermodynamically unchanged) equilibrium state is observed.

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Besides the advantage of a very gentle displacement of concentrations the method according to the invention has, in comparison to conventional relaxation methods, the further advantage to be technically particularly easy to implement since all that is needed to establish the non-equilibrium state is a controllable light source. Due to the easiness of its setup the method is also suited for use in portable devices for fast in-situ measurement, e.g. when searching particular chemical substances affecting the kinetics of a reaction."

B) Regarding the rejection of claims 1-3 and 7-13 under 35 U.S.C. 102(b) as anticipated by Giordano et al., Applicants argue the following:

i) Giordano et al. do not teach generating a non-equilibrium state of a chemical reaction and observing by means of a fluorescence signal, at least one portion of a relaxation of concentrations of the species involved.

ii) Applicants repeat the description of the invention given in the arguments regarding enablement rejection.

C) Regarding the rejection of claims 4-6 under 35 U.S.C. 103(a) over Giordano et al. and Watrob et al., Applicants argue that these claims are allowable because claim 1, from which they depend, is allowable.

Regarding A), examiner is thankful to Applicants for an extensive review of FRET literature. However, the FRET measurement is not an issue in the enablement rejection. The issues, as detailed in the rejection are:

i) Lack of evidence (either in the disclosure or in the prior art) that in any chemical reaction a concentration of reactants can be perturbed by impinging light on the reaction. For example, let us

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imagine a hybridization reaction between a target nucleic acid and FRET-labeled probe. The reaction can be perturbed by adding additional reactants, changing temperature or pH, but there is no evidence that merely illuminating the reaction with a light which enables observation of the FRET effect between fluorescent donor and acceptor has any effect on the kinetics of hybridization of the two nucleic acids. The fact that light stimulates a population of fluorescent acceptors bound to DNA has no bearing on the DNA hybridization kinetics. Similar arguments can be advanced for proteins, peptides, etc. Further, as explained in the rejection, the only molecules that might be subject to perturbation of their concentrations by light are fluorophores themselves.

ii) Lack of evidence of how any "kinetic quantity" can be derived from such a measurement.

None of the references cited by Applicants provide evidence that using light to observe FRET effects in biological systems causes perturbation of reactant concentrations and can be used to measure "kinetic quantities" in such reactions. Finally, Applicants' statement that the method relies on "an *inversion of the principles of application of conventional measurements of relaxation kinetics*" is not backed up with any evidence that such principle actually works as claimed.

The rejection is maintained.

Regarding B), Applicants did not define the terms "non-equilibrium state", therefore, any state of the reaction can be considered to be "non-equilibrium". Giordano et al. clearly observe the non-equilibrium state of the conversion between the two forms of the diheteroarylethenes, as shown in Fig. 4. Therefore Giordano et al. explicitly teach the claimed method.

The rejection is maintained.

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Regarding C), the arguments regarding patentability of claim 1 were addressed above.

The rejection is maintained.

Claim Interpretation

4. The term “characteristic kinetic quantity of a chemical reaction” has not been defined by Applicants, therefore it is interpreted as any measurable variable.
5. The term “species including at least one fluorophore” is interpreted as any molecule which comprises at least one fluorophore, involved in any chemical reaction.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for monitoring chemical reactions in which the chemical species are fluorophores themselves and in which the physical or chemical properties of the fluorophores are changed upon irradiation with light in such a way as to create populations of molecules in two different states where the populations of molecules are different from the populations before the irradiation, does not reasonably provide enablement for monitoring chemical reactions with any molecule having a fluorophore attached to it in any other chemical reaction. In addition, there is no enablement for determining any kinetic quantity of any chemical reaction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and breadth of claims

Claims 1-13 are broadly drawn to a method for determining a characteristic kinetic quantity of a chemical reaction in a sample involving a plurality of chemical species, at least one of said species including at least one fluorophore, the method comprising the steps of:

generating, by impinging light on said sample, a non-equilibrium state of said chemical reaction, and observing, by means of a fluorescence signal of at least one fluorophore, at least one portion of a relaxation of concentrations of said species involved, the method wherein at least one product of said chemical reaction under test comprises a combination of two species each of which including one partner of a FRET pair consisting of a FRET donor and a FRET acceptor wherein said FRET acceptor is a photochrome, the absorption spectrum of which being changeable by irradiation with light of a suitable wavelength; wherein said FRET donor is a fluorophore, the emission spectrum of which having an overlap region with said FRET acceptor's absorption spectrum, the size of said overlap region being dependent on the photochromic state of said FRET acceptor; and wherein said light used for generating said non-equilibrium state has a wavelength capable of switching said photochromic state of said FRET acceptor.

However, as will be further discussed, there is no support in the specification and prior art for the full scope of the claimed method. The invention is a class of invention which the CAFC has

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characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has no working examples of how to determine any kinetic parameters of any chemical reaction, even one involving just fluorophores themselves. There are no examples of how to determine kinetic parameters of any other reaction in which molecules are labeled with fluorophores.

Guidance in the Specification.

The specification provides no evidence that the disclosed use of photochromic FRET acceptor molecules provides means for detecting any kinetic quantity of a chemical reaction, for example, a rate constant. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. Applicants did not show that light can cause deviation from equilibrium concentrations of any chemical species in any chemical reaction in which the products are labeled with photochromic acceptors, except the photochromic acceptors themselves.

The unpredictability of the art and the state of the prior art

The only example found in literature for use in determining reaction rates is Giordano et al. (*J. Am. Chem. Soc.*, vol. 124, pp. 7481-7489, 2002; cited in the IDS), in which the photoconversion rates of diheteroarylethene compounds bound to Lucifer Yellow cadaverine were determined using light-induced conversion of diheteroarylethene between two different states, open and closed.

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There are no examples in literature how light irradiation could cause a change in concentration of chemical reaction participants in any reaction which does not involve the photochromic acceptors themselves, since even in the case of the acceptors attached to a DNA, for example, irradiating the reaction with light would cause a change in the state of the acceptors, but not in the state of the DNA molecules to which they were attached, i.e., in the case of hybridization reaction between a population of DNA molecules labeled with an acceptor and a second population labeled with a donor, irradiating the reaction with light would not change the concentrations of these two types of DNA populations. Therefore, the rate constants for hybridization could not be determined from such measurement. Further examples of macromolecular systems in which such process would not work are protein-DNA binding, for example, as presented by Kozlov et al. (Biochemistry, vol. 41, pp. 6032-6044, 2002; cited in the previous office action), protein-substrate interactions, as detailed by Takakusa et al. (J. Am. Chem. Soc., vol. 124, pp. 1653-1657, 2002; cited in the previous office action) or protein-membranes interactions, as referenced by Hamman et al. (J. Biomol. Screening, vol. 7, pp. 45-55, 2002; cited in the previous office action). Since there are literally billions of potential chemical reactions using molecules labeled with fluorescent donors and acceptors, the above examples are only a minute fraction.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this technology to detection of kinetic parameters of any chemical reaction in which participating molecules are labeled with fluorescent acceptor and donor molecules, including determining which molecules aside from the photochromes themselves undergo physical or chemical changes in the presence of light of any

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wavelength, and how such kinetic constants can be determined. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the kinetic parameters of a large percentage of chemical reactions cannot be measured by perturbing the equilibrium state of the reaction with light, the factor of unpredictability weighs heavily in favor of undue experimentation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-3 and 7-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Giordano et al. (J. Am. Chem. Soc., vol. 124, pp. 7481-7489, 2002; cited in the IDS and in the previous office

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action) as evidenced by the Supplemental material (J. Am. Chem. Soc., vol. 124, 2002; cited in the previous office action).

Regarding claim 1, Giordano et al. teach a method of determining characteristic kinetic quantity of a chemical reaction in a sample involving a plurality of chemical species, at least one of said species including at least one fluorophore (Fig. 1; page 7482, last paragraph; page 7483, first paragraph; Table 1; page 7485, second paragraph; page 7486, paragraphs 1-3), the method comprising the steps of:

generating, by impinging light on said sample, a non-equilibrium state of said chemical reaction (page 7483, paragraphs 1-4; Fig. 4), and

observing, by means of a fluorescence signal of at least one fluorophore, at least one portion of a relaxation of concentrations of said species involved (Fig. 4),

the method wherein at least one product of said chemical reaction under test comprises a combination of two species each of which including one partner of a FRET pair consisting of a FRET donor and a FRET acceptor wherein said FRET acceptor is a photochrome, the absorption spectrum of which being changeable by irradiation with light of a suitable wavelength (Fig. 1; page 7482, paragraphs 3-8);

wherein said FRET donor is a fluorophore, the emission spectrum of which having an overlap region with said FRET acceptor's absorption spectrum, the size of said overlap region being dependent on the photochromic state of said FRET acceptor (Fig. 1; page 7482, 7th paragraph);

and wherein said light used for generating said non-equilibrium state has a wavelength capable of switching said photochromic state of said FRET acceptor (Fig. 1; page 7482, paragraphs 5-8).

Regarding claim 2, Giordano et al. teach detecting the fluorescence of the donor (Fig. 2).

Regarding claim 3, Giordano et al. teach detection of the fluorescence of the acceptor (Fig. 3, 4).

Regarding claim 7, Giordano et al. teach the first and second directions of the reaction excited by two different wavelengths (Fig. 1; Table 1).

Regarding claim 8, Giordano et al. teach UV light (Fig. 1; Table 1).

Regarding claims 9 and 10, Giordano et al. teach irradiation with visible light (Fig. 1; Table 1).

Regarding claim 11, Giordano et al. teach that the intensity of irradiation used for photoconversion is higher than the intensity of irradiation used for fluorescence measurement (Supplemental material page 5, last paragraph; page 6, first and second paragraphs).

Regarding claims 12 and 13, Giordano et al. teach irradiating the sample in a temporally modulated fashion using two different wavelengths (Fig. 6).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giordano et al. (J. Am. Chem. Soc., vol. 124, pp. 7481-7489, 2002; cited in the IDS and in the previous office action) as evidenced by the Supplemental material (J. Am. Chem. Soc., vol. 124, 2002; cited in the previous office action) and Watrob et al. (J. Am. Chem. Soc., vol. 125, pp. 7336-7343, May 2003; cited in the previous office action).

A) Regarding claims 4-6, Giordano et al. teach a system with one acceptor and one donor, but do not teach a system with an additional acceptor.

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B) Regarding claims 4-6, Watrob et al. teach using a system with one donor and two acceptors (Scheme 1; page 7337, 7338).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used additional acceptor of Watrob et al. in the method of Giordano et al. The motivation to do so is provided by Watrob et al., who state (page 7342, last paragraph):

“Three-chromophore FRET systems offer several advantages. First, three-chromophore systems report the simultaneous proximity of three species and provide the ability to measure two or three distances in a complex. Structural information about the assembly can then be inferred from the relative positions of individual components of the complex. For example, in Case I where no FRET 1 → 3 occurs, r_{13} must be $>1.5 R_{013}$. This restricts the position of **3** relative to **1** to a minimal distance of $r_{13} \sim 1.75 R_{013}$ and a maximal distance of $r_{13} = r_{12} + r_{23}$ for a linear arrangement of **1**, **2**, and **3**. Second, in the case of linear or near linear arrangement of the three chromophores, two-step FRET extends the distance range for detection of simultaneous proximity. For example, assuming $R_0 = 55 \text{ \AA}$ for the two FRET pairs and a detection limit of $1.5 R_0$, one-step FRET at a distance $r = 83 \text{ \AA}$ has an efficiency $E_{ij} = 0.08$. A two-step FRET relay with $E_{\text{relay}} = 0.08$ corresponds to a total distance $r = 127 \text{ \AA}$. Thus, the detectable distance range increases by as much as 50%. Third, three-chromophore systems require fewer labeled samples to measure two or three distances than conventional one-step FRET.”

12. No claims are allowed.

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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